Sir, SSc is a multisystem autoimmune disorder characterized by distinctive vascular abnormalities, immune dysfunction and fibrosis of skin and internal organs. The two major subtypes, limited cutaneous SSc (LSSc) and diffuse cutaneous SSc (DSSc), are defined on the basis of the extent of the cutaneous involvement and have different natural histories, patterns of internal organ involvement and prognoses [1]: as a generalization, vascular abnormalities are more pronounced in LSSc. Although recent advances have improved our understanding of SSc disease pathogenesis, much remains unknown.

Endothelial dysfunction forms an integral part of vasculopathy in SSc. Endothelial cells produce many humoral factors, which are capable of activating the immune-mediated response. VEGFs are a series of growth factors (VEGF-A, VEGF-B, VEGF-C, VEGF-D and orf virus VEGF) essential for vascular and lymphatic growth, and are secreted by the endothelial cells [2]. Whilst VEGF-A and VEGF-D are markers of angiogenesis and vasculopathy, VEGF-C is a specific marker of lymphangiogenesis. VEGF-C and lymphangiogenesis have been extensively studied and implicated in various malignancies, including gastrointestinal and colorectal malignancies [3] and chronic inflammation [4]. Abnormal angiogenesis and VEGF-A (a serum marker of angiogenesis) have been studied and implicated in the pathogenesis of SSc [5, 6]. Although lymphatic microangiopathy has been demonstrated in the skin of SSc patients [7], we are not aware of any previous reports examining VEGF-C (and thus lymphangiogenesis) in SSc. The aim of our study was to test the hypothesis that circulating levels of VEGF-C (a soluble serum marker of lymphangiogenesis) are abnormal in SSc patients. This study was approved by the Salford and Trafford Research Ethics Committee. All patients signed a written informed consent.

Sera from 52 unselected SSc patients and 81 healthy controls of similar age and gender were collected and stored at −70°C. Of 52 SSc patients, 38 had LSSc and 14 had DSSc. The mean age and range for LSSc, DSSc and healthy controls were 61 yrs (35–83 yrs), 57 yrs (26–81 yrs) and 60 yrs (42–73 yrs), respectively. There were 32 females and six males in the LSSc group, nine females and five males in the DSSc group and 61 females and 20 males in the control group.

VEGF-C level was measured in all samples with ELISA, developed in our laboratory, with high specificity and sensitivity for detecting VEGF-C, with no cross-reaction with VEGF-A or VEGF-D [4].

Data were non-normally distributed and hence were analysed using Mann–Whitney U-test.

Circulating levels of VEGF-C were significantly higher in SSc patients (combining the two subgroups, LSSc and DSSc) as compared with controls ($P < 0.001$) (Fig. 1A).

Subgroup analysis showed that VEGF-C levels were higher in both LSSc, ($P < 0.001$) (Fig. 1B) and DSSc patients ($P = 0.022$) (Fig. 1C) compared with controls.

There was no statistically significant difference in serum VEGF-C between LSSc and DSSc subgroups, ($P = 0.793$) (Fig. 1D).

**Fig. 1.** Box and whisker plots comparing VEGF-C levels between groups. Boxes represent the interquartile range, whiskers represent highest and lowest values excluding the outliers and circles represent the outliers. (A) Serum VEGF-C in SSc patients vs controls ($P = 0.001$). (B) Serum VEGF-C levels in LSSc patients vs controls ($P < 0.001$). (C) Serum VEGF-C levels in DSSc patients vs controls ($P = 0.022$). (D) Serum VEGF-C levels in patients with LSSc vs DSSc ($P = 0.793$).
To our knowledge this is the first study to suggest abnormal lymphangiogenesis in SSc. This was a small pilot study and our findings need to be confirmed in larger studies. Emerging evidence suggests that chemokines such as TNF-α and NF-κB, and macrophages are involved in the proliferation and differentiation of lymphatic endothelial cells (LEC) and may play an important role in inflammatory lymphangiogenesis [8]. Although the mechanisms and consequences of abnormal lymphangiogenesis in SSc are unclear, increased understanding of LEC-specific modulators in the inflammatory microenvironment and of the molecular mechanisms controlling the growth of lymphatic vessels may allow us to develop new therapeutic targets [9], similar to bevacizumab (anti-VEGF-A antibody) that was developed to target angiogenesis, in cancer therapy [10].

**Rheumatology key message**

- Circulating levels of VEGF-C are raised in SSc and suggest abnormal lymphangiogenesis.

**Disclosure statement:** The authors have declared no conflicts of interest.

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**Vasa-vasoritis of the aorta and fatal myocarditis in fulminant Churg–Strauss syndrome**

Sir, We report a fulminant case of Churg–Strauss syndrome (CSS) with fatal myocarditis, and atypical aortitis with vasa-vasorum involvement.

CSS is a small-sized vessel necrotizing vasculitis, characterized by late-onset asthma and blood eosinophilia. All organs may be involved, but severe gastrointestinal, renal, cardiac and central nervous system manifestations are associated with a poor prognosis [1].

A 42-yr-old patient was admitted into our institution with a 3-day history of abdominal pain without intestinal bleeding. He was complaining of worsening asthma and nasal polyps. The physical examination was unremarkable, except for sinus tachycardia.

On day 3 of hospitalization, the patient died suddenly in ventricular fibrillation. CSS was confirmed at the time of autopsy, revealing a necrotizing myocarditis due to medium-sized vessel vasculitis, with a large eosinophilic infiltrate. There was no evidence of coronaryitis. The lungs and liver were also involved, but the intestinal tract and kidneys were normal. Moreover, histological examination of the aorta revealed aortitis with granulomatous and necrotizing angiitis of the vasa-vasorum (Fig. 1).

Cardiac manifestations are common in CSS and are associated with a poor prognosis [1]. As in our patient, myocardial involvement is a major cause of death [2] and is usually associated with an ANCA-negative status [3].

This case was remarkable because aortitis was noted at the time of autopsy. To our knowledge and in contrast with other ANCA-associated vasculitides [4–9], aortitis has never been reported in association with CSS. Our observation demonstrates that aortitis in CSS is specifically due to involvement of the vasa-vasorum (small-sized vessels), in agreement with the pathogenic hypothesis advanced by Nakabayashi et al. [4] in other ANCA-associated vasculitides. Vasa-vasoritis of the aorta has also been reported in bacterial septicaemia (e.g. *Staphylococcus aureus*, non-typified *Salmonella* spp. and *Treponema pallidum*) [7, 10]. The lesions we observed were quite different from aortitis occurring in GCA, Takayasu arteritis or the aortitis associated with rheumatic disorders. The lesions appeared closer to Behçet’s aortitis involving the media and adventitia.

Clinicians must always be aware of cardiac manifestations of vasculitis, especially in patients with CSS. Aorta can be involved in small-sized vasculitis because of vasa-vasorum involvement.

**Rheumatology key message**

- We describe the first case of aortitis in CSS, necropsy proven, due to vasa-vasoritis involvement.

**FIG. 1. Vasa-vasoritis of the aorta with granulomatous and necrotizing angiitis.**

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